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Mechanism and Stereoselectivity of the Stepwise 1,3-Dipolar Cycloadditions between a Thiocarbonyl Ylide and Electron-Deficient Dipolarophiles: A Computational Investigation

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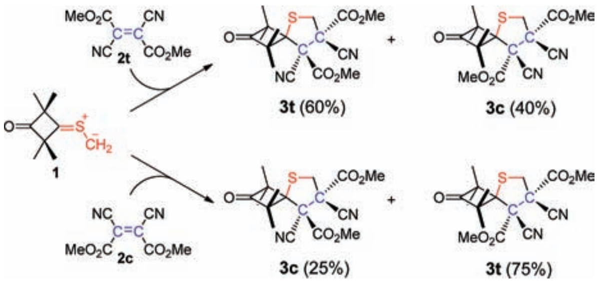
Abstract: The 1,3-dipolar cycloadditions of a thiocarbonyl ylide to dimethyl 2,3-dicyanofumarate and 2,3-dicyanomaleate have been studied with DFT computations. The first C−C bond is formed via an *anti* attack to produce a very polar, zwitterionic diradical. The low stereoselectivity of the reaction was found to arise from rotations about single bonds in the intermediates that compete with cyclization. A distortion−interaction energy analysis was performed to compare the stepwise and concerted mechanisms, and to explain why the stepwise mechanism is favored in this unusual case.

Introduction

The 1,3-dipolar cycloaddition reactions, established and systematically studied by Huisgen,[1] serve as a powerful tool for the synthesis of heterocycles.[2] The mechanism of these reactions—concerted or stepwise—was hotly debated in the 1970s and 1980s, but most of these reactions have been determined to be concerted.[3] Huisgen, Mloston, and Langhals surprised the chemical community in 1986, showing that the reaction of a thiocarbonyl ylide with a highly electron-deficient dipolarophile was non-stereospecific, thus establishing a stepwise mechanism for this reaction.[4] Since then, this reaction has attracted computational studies. Sustmann and Huisgen, and Domingo and Picher, have confirmed the stepwise nature of related model reactions by computations.[5] Here, we explore the reactions studied by Huisgen, explain why this reaction is stepwise even though other closely related 1,3-dipolar cycloaddition reactions of this type are concerted,[6] and show the mixed diradical[7] and zwitterionic[8] nature of the intermediate.

Scheme 1. Experimental Observations by the Huisgen Group[10]



Background

As shown in Scheme 1, Huisgen reported that the reaction of thiocarbonyl methylide **1** with dimethyl dicyanofumarate **2t** in chloroform at 80 °C gives both *trans*-**3t** and *cis*-**3c** products. The *trans*/*cis* ratio is 60:40. When dimethyl dicyanomaleate **2c** is used as the dipolarophile, the *cis*/*trans* ratio becomes 75:25.[9] The ratio increases slightly with solvent polarity.[9b] This observation indicates a stepwise mechanism for the 1,3-dipolar

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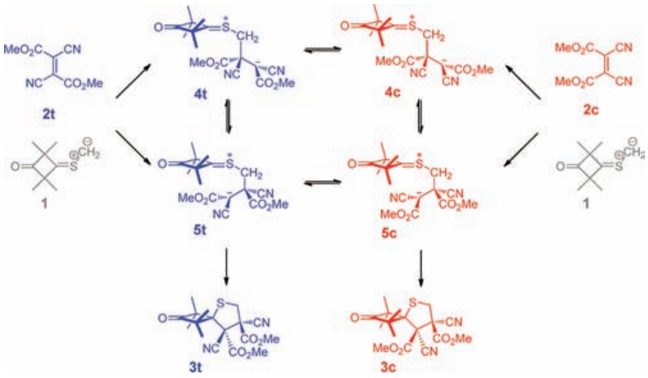
Scheme 2. Stepwise Mechanism Proposed by Huisgen[a]



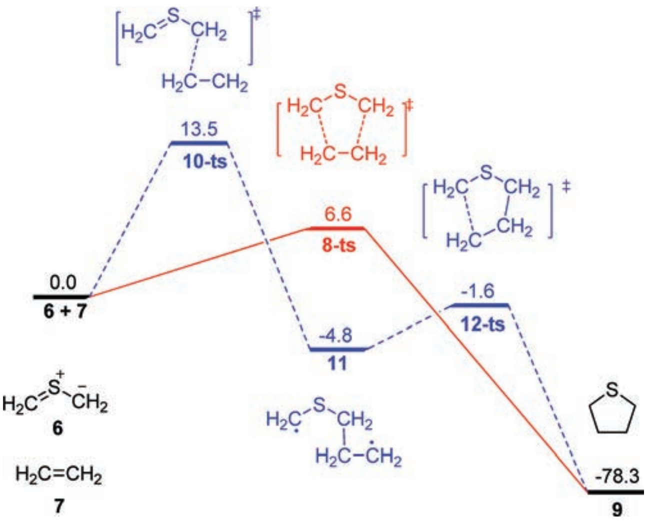
[a] The *trans*-alkenes and intermediates are shown in blue. The *cis*-alkenes and intermediates are shown in red.

cycloaddition reaction between this thiocarbonyl ylide and these electron-deficient dipolarophiles.[10]

The mechanism shown in Scheme 2 was proposed by Huisgen.[11] The ylide **1** attacks the dipolarophile **2t**, generating the *anti* zwitterion, **4t**, or the *gauche* conformation, **5t**. Rotation around single bonds of the intermediate **4t** leads to **4c** or **5t**. The second C−C bond formation from **5t** irreversibly generates the *trans* product **3t**. Bond rotation of the zwitterion intermediate **4c** leads to **5c**, along with the side product **3c**. Similarly, when 1,3-dipole **1** reacts with the dipolarophile **2c**, the 1,3-dipolar cycloaddition involves the same intermediates.

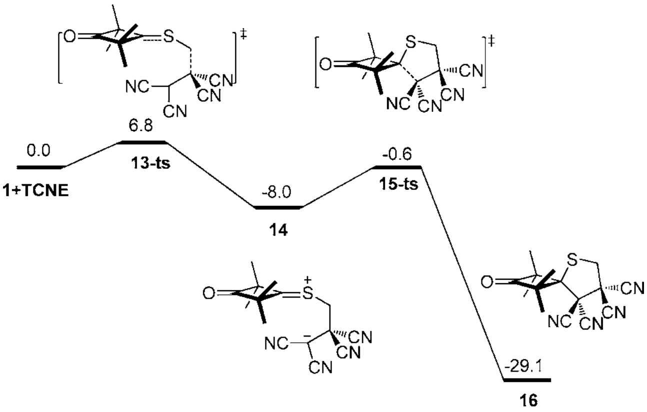
In previous DFT[12] and molecular dynamics[13] calculations, simple 1,3-dipolar cycloadditions were found to follow a concerted pathway. Although there are many reports of dipolar cycloadditions of thiocarbonyl ylides,[14] none of them clearly show a concerted pathway. Sustmann and Huisgen previously used DFT to investigate the reaction of thioformaldehyde methylide with ethylene (Scheme 3).[15] The concerted transition state, **8-ts**, is 7 kcal/mol lower than the transition state **10-ts** leading to the diradical intermediate. The authors used the CASPT2 method to calculate the biradical character of the intermediates and transition states. They found that the thiocarbonyl ylide **6** shows 24% biradical character and the intermediate **11** shows 84% biradical character.

Scheme 3. Summary of Sustmann's DFT Calculation on the Competition between Concerted and Stepwise Mechanisms with Thioformaldehyde Methylide and Ethylene[a]



[a] The values are the relative (U)B3LYP energies (kcal/mol) with zero-point vibrational correction.

Scheme 4. Summary of Domingo's DFT Calculation on the Stepwise Mechanism of Dipolar Cycloaddition with **1** to Tetracyanoethylene[a]



[a] The values are the relative free energies at the B3LYP/6-31G* level.

Domingo et al. reported a DFT study of the 1,3-dipolar cycloaddition of Huisgen's thiocarbonyl ylide to tetracyanoethylene (TCNE) (Scheme 4).[5] Two significant conclusions are drawn: (a) the reaction has a stepwise mechanism as a consequence of steric hindrance associated with the formation of the second C−C σ bond, in clear agreement with Huisgen's proposal, and (b) the reaction has a high zwitterionic character as a consequence of the high electrophilic character of TCNE and the potent nucleophilic character of the corresponding thiocarbonyl ylide **1**. The authors argued that the large electrophilicity difference between thiocarbonyl ylide **1** and TCNE leads to the generation of the zwitterion intermediate **14**. However, the character of the stepwise intermediate, zwitterion or biradical, was not described except to note the extent of charge transfer from dipole to dipolarophile.

Computational Methods

All the DFT calculations were carried out with the GAUSSIAN 03[16] series of programs. Unrestricted density functional theory (U)B3LYP[17] with a standard 6-31+G(d) basis set was used for geometry optimizations. Harmonic frequency calculations were

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performed for all stationary points to confirm them as local minima or transition structures and to derive the ZPEs and thermochemical corrections for the enthalpies and free energies. The solvent effects were considered by single-point calculations on the gas-phase stationary points with an integral equation formalism polarizable continuum model (IEFPCM).[18] Chloroform was the solvent. The molecular cavities were built up using the United Atom Topological Model (UAHF), which was reported to be more accurate than cavity models such as UFF, Pauling, or Bondi.[19]

The relative rate constants k_1/k_2 can be described by Eyring transition-state theory:

$$k_1/k_2 = \mathrm{e}^{-(\Delta G^{\ddagger}{}_1 - \Delta G^{\ddagger}{}_2)/RT} \tag{1}$$

The free energies consist of both enthalpy and entropy parts:

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \tag{2}$$

In the DFT calculation, the calculated entropy data are sometimes less accurate than calculated enthalpy because of low-frequency vibrational modes[20] and because there may be additional conformers that would contribute to the entropy.[21] In addition, the computation of solvation entropy change from standard thermodynamic formulas has been found to be difficult.[22] For the stereoselectivity-determining steps, all the reactions are unimolecular. Thus, the relative activation entropies should be close to zero. We tested the use of both computed free energies and the free energies obtained from enthalpies by assuming the entropy change is zero (eq 3).

$$k_1/k_2 = \mathrm{e}^{-(\Delta H^{\ddagger}{}_1 - \Delta H^{\ddagger}{}_2)/RT} \tag{3}$$

We have evaluated the diradical character of various species using valence bond (VB) theory,[23] a powerful tool to calculate the weights of VB structures for 1,3-dipoles.[24] Here the D-BOVB[25] level calculation is used to calculate the weights of VB structures for the thiocarbonyl ylide **1** to analyze biradical character. The VB calculations were carried out with the Xiamen VB (XMVB) package.[26]

Results and Discussion

1. Diradical Character of the Thiocarbonyl Ylide 6. Braida et al. have shown that the reactivities of 1,3-dipoles in 1,3-dipolar cycloadditions are qualitatively related to the diradical character of the 1,3-dipole.[24] The VB structures for the model thiocarbonyl ylide **6** are shown in Figure 1. There are six VB structures for the thiocarbonyl ylide **6**. The weight of diradical VB structure **6-1** is largest. The thiocarbonyl ylide **6** shows 54% diradical character. The weight of the sum of the traditional all-octet dipolar VB structures **6-2** and **6-3** is 39%. The weight of VB structures shows that the thiocarbonyl ylide **6** has both diradical and zwitterionic character. The diradical reaction found by Sustmann for the parent is consistent with the highly reactive diradical character of **6**.

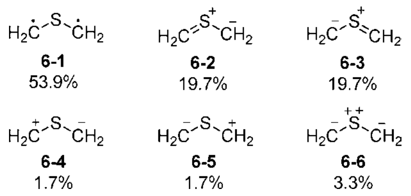

Figure 1. Weight of VB structures for the thiocarbonyl ylide **1**.

Table 1. Relative Enthalpies and Free Energies (kcal/mol) Calculated in the Gas Phase and in Chloroform Solvent

	gas phase		chloroform	
	ΔH	ΔG	ΔH	ΔG
1 + 2c	0.0	0.0	0.0	0.0
1 + 2t	0.7	0.0	−0.3	−1.0
3c	−35.2	−16.8	−35.3	−16.8
3t	−42.0	−23.2	−41.3	−22.5
4c	−14.8	−0.4	−17.7	−3.3
4t	−15.1	−0.3	−17.8	−3.0
5c	−12.5	1.9	−14.9	−0.5
5t	−12.9	1.7	−15.9	−1.3
17c-ts	3.2	17.2	2.2	16.2
18c-ts	−0.9	12.5	−0.1	13.4
18t-ts	−0.8	13.1	−1.7	12.2
19c-ts	−9.2	6.4	−12.4	3.3
19t-ts	−7.6	7.5	−11.9	3.2
20c-ts	−12.9	4.1	−14.5	2.5
20t-ts	−11.7	5.6	−13.0	4.3
21-ts	−6.5	8.6	−11.7	3.4
22-ts	−3.7	12.7	−7.0	9.4

2. *Gauche* and *Anti* Attack. The thiocarbonyl ylide **1** can react with electron-deficient dipolarophiles, **2c** or **2t**, to give the *gauche* conformations, **5c** or **5t**, or the *anti* conformation, **4c** or **4t**. The *anti* conformations, **4c** or **4t**, and the *gauche* conformations, **5c** or **5t**, can interconvert. Computations were carried out to investigate these reaction pathways. Calculated energies are given in Table 1.

As shown in Figure 2, the reaction of **1** with **2c** proceeds preferentially via transition state **18c-ts**. The activation free energy for *anti* attack is 13.4 kcal/mol (enthalpy is −0.1 kcal/mol). The *anti* conformation **4c** is 3.3 kcal/mol ($\Delta H = -17.7$ kcal/mol) lower than **2c + 1**. The *anti* conformation **4c** can then undergo reversible internal rotation to the *gauche* conformation **5c** via transition state **19c-ts** with a barrier of only 6.6 kcal/mol ($\Delta H = 5.3$ kcal/mol). The *gauche* conformation **5c** also can be formed directly via the transition state **17c-ts**, but

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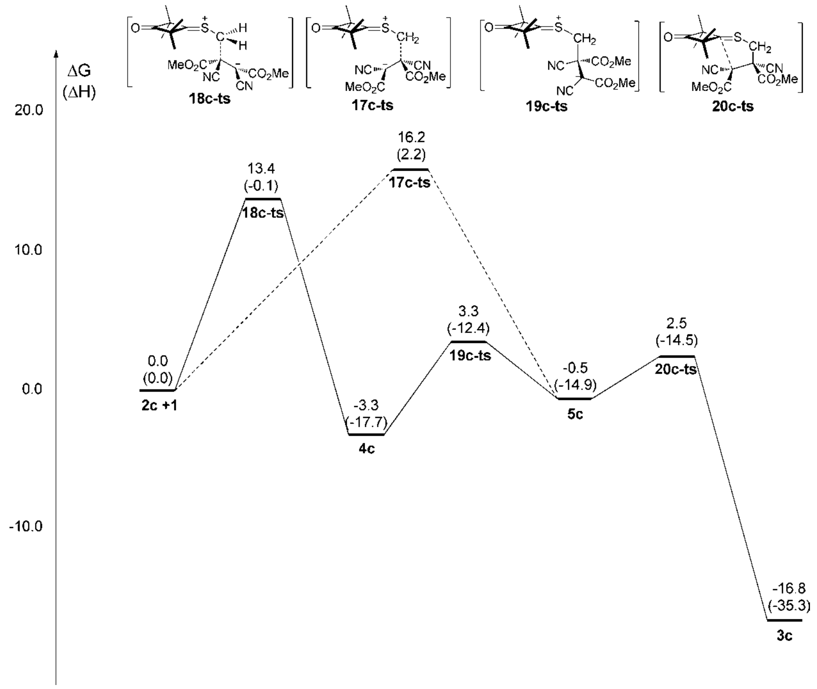

Figure 2. Pathways for reaction of **1** with **2c** with retention of stereochemistry. Free energies in $CHCl_3$ are given. Relative enthalpies (corrected by $CHCl_3$ solution free energies) are given in parentheses.

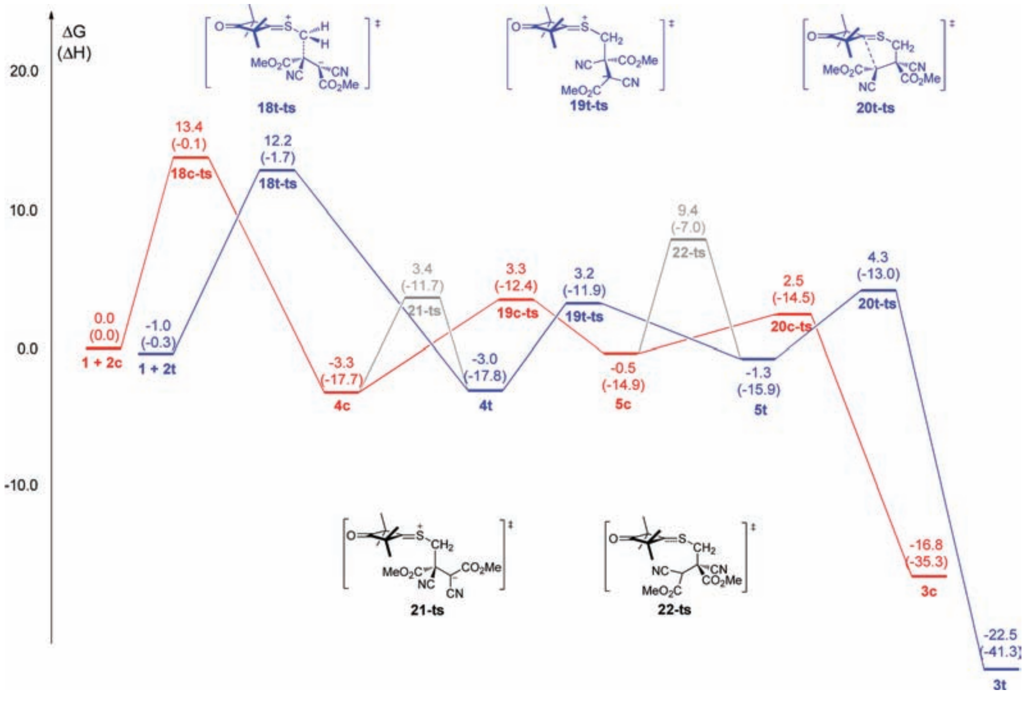

Figure 3. Free energy profile of the dipolar cycloaddition of thiocarbonyl ylide **1** with dicyanofumarate and dicyanomaleate. Energies include $CHCl_3$ solution. Enthalpies with solvation correction are in parentheses.

the activation free energy for *gauche* attack is 16.2 kcal/mol ($\Delta H = 2.2$ kcal/). The relative free energy of the transition state **17c-ts** is 2.8 kcal/mol ($\Delta H = 2.3$ kcal/mol) higher than the transition state **18c-ts**. Therefore, the first C−C bond formation leads preferentially to the *anti* conformation, **4c**. Rotation about the newly formed C−C bond can lead to the *gauche* conformation **5c**. The second C−C bond forms via the transition state **20c-ts**. The formation of the second C−C bond has a barrier of only 3.0 kcal/mol ($\Delta H = 0.4$ kcal/mol). The *cis* product **3c** is formed irreversibly. The energies are influenced to a large extent by solvation; in particular, the formation of zwitterions becomes highly exothermic, but the relative energies of intermediates are maintained.

3. Complete Pathway for the Dipolar Cycloaddition of Huisgen's Thiocarbonyl Ylide with Dicyanofumarate and Dicyanomaleate. In experiments by Huisgen et al.,[4] both the *cis* and *trans* products were observed from either pure dimethyl dicyanomaleate **2c** or dimethyl dicyanofumarate **2t**. To understand why there is some stereoselectivity in these reactions, we calculated the whole potential energy profile.

As shown in Figure 3, for both dipolarophiles **2c** and **2t**, the rate-determining step is the formation of the first C−C bond. The activation enthalpy of the reversible isomerization of **4c** to **4t** is only 6.0 kcal/mol via the transition state **21-ts**. The barriers for isomerization of the zwitterions intermediates are all quite low.

The activation barrier for *anti*-to-*gauche* isomerization for **4c** and **4t** is lower than for the *cis*-to-*trans* interconversion of the intermediates. That leads to some retention of stereochemistry. The geometries of the intermediates and transition states are shown in Figure 4.

4. Stereoselectivity. The stereoselectivity was computed from rate constants for the processes shown in Figure 5.

From dicyanomaleate, **2c**, the intermediate **4c** is generated directly. The steady-state approximation gives eqs 4−6 from various processes.

$$k_1[\mathbf{4c}] + k_{-3}[\mathbf{5t}] = (k_{-1} + k_3)[\mathbf{4t}] \tag{4}$$

$$k_2[\mathbf{4c}] = (k_{-2} + k_4)[\mathbf{5c}] \tag{5}$$

$$k_3[\mathbf{4t}] = (k_{-3} + k_5)[\mathbf{5t}] \tag{6}$$

Based on eqs 4−6, the formation rate of the products **3c** and **3t** is shown as eq 7. All the rate constants were computed directly from free energies or from ΔH values, assuming ΔS = 0. As shown in Table 2, when the free energies in solvent or these enthalpies corrected by solvation free energies are used to calculate the rate constants, the predicted ratio of **3c**/**3t** is 82:18−84:16, close to the experimental observation (75:25).

$$\frac{[\mathbf{3c}]}{[\mathbf{3t}]} = \frac{k_2k_4(k_{-1} + k_3)(k_{-3} + k_5) - k_2k_3k_{-3}k_4}{k_1k_3k_5(k_{-2} + k_4)} \tag{7}$$

Correspondingly, starting from dicyanofumarate **2t**, the formation and consumption rates of intermediates **4c**, **5c**, and **5t** are the same, leading to eqs 5, 2, and 3.

$$k_{-1}[\mathbf{4t}] + k_{-2}[\mathbf{5c}] = (k_1 + k_2)[\mathbf{4c}] \tag{8}$$

$$k_2[\mathbf{4c}] = (k_{-2} + k_4)[\mathbf{5c}] \tag{5}$$

$$k_3[\mathbf{4t}] = (k_{-3} + k_5)[\mathbf{5t}] \tag{6}$$

Based on eqs 8, 5, and 6, the ratio of formation of **3t** and **3c** is shown as eq 9. When enthalpies corrected by solvation are used to calculate the rate constants, the predicted selectivity of **3t**/**3c** is 61:39, while free energies are slightly less satisfactory, 69:31.

$$\frac{[\mathbf{3t}]}{[\mathbf{3c}]} = \frac{k_3k_5(k_{-2} + k_4)(k_1 + k_2) - k_2k_{-2}k_3k_5}{k_1k_2k_4(k_{-3} + k_5)} \tag{9}$$

With gas-phase free energies, the major product coincides with the experimental results, but the stereoselectivity is predicted to be higher in both cases.

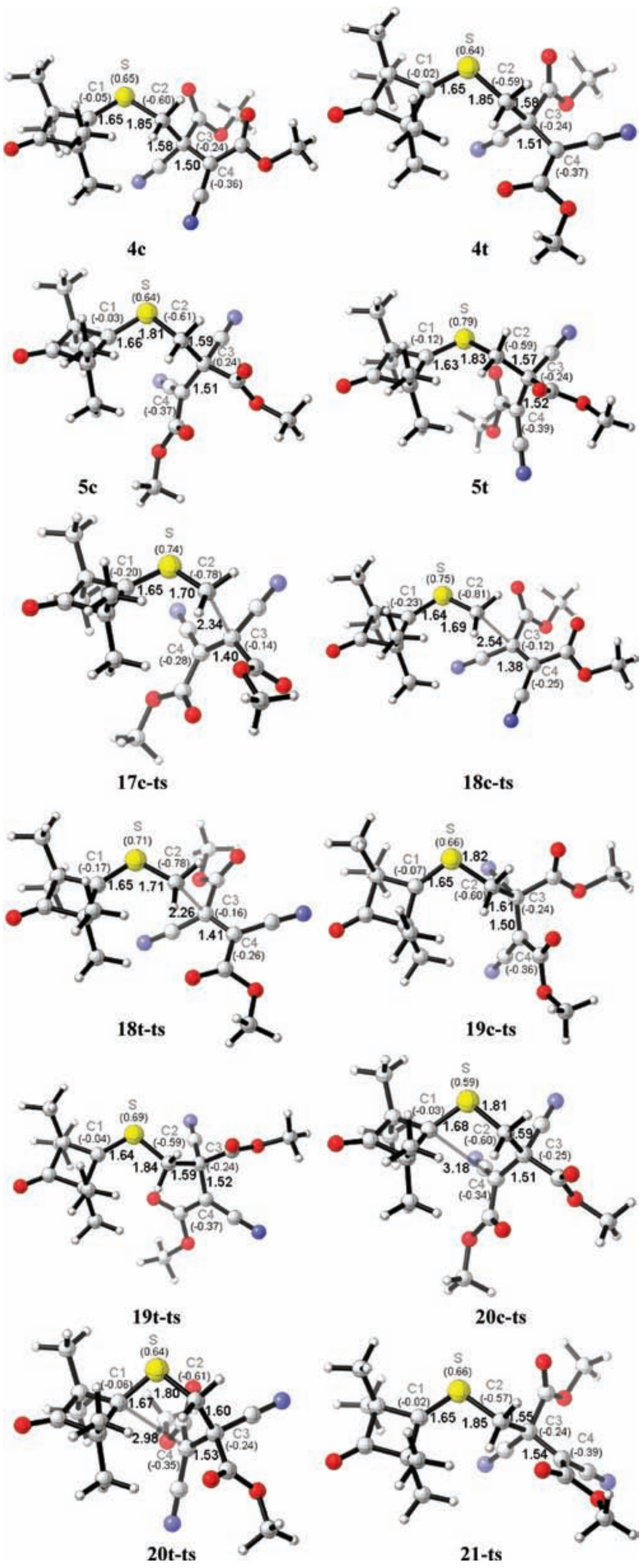

Figure 4. The geometries of the intermediates and transition states.[27] The natural population analysis (NPA) charges are given in parentheses.

5. Electronic Structures. The computed stepwise mechanism is in good accord with experiment. To explore the nature of the intermediates in detail, the electrostatic potential (ESP), natural bonding orbital (NBO) charge analysis, and the electronic structures of the ground and excited states were carried out for both the *anti* and *gauche* intermediates **4c**, **4t**, **5c**, and **5t**. The ESPs of **4c**, **4t**, **5c**, and **5t** (Figure 6) clearly indicate charge separation. The largest positive charge density (shown in Figure 4) resides on the sulfur atom. The negative charge is localized on the dipolarophile part of the intermediate. The negative charge is mostly localized on the cyano and ester groups.

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(27) Prepared using CYLView: Legault, C. Y. *CYLview*, 1.0b; Université de Sherbrooke: Quebec, 2009; http://www.cylview.org.

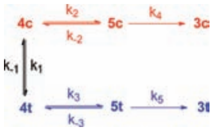

Figure 5. The rate constants for isomerization and ring closure steps.

Table 2. Product Percentage from Experimental Observations and Theoretical Calculations

	experiment		calc (solv, ΔH)		calc (solv, ΔG)		calc (gas, ΔH)	
	2c	**2t**	**2c**	**2t**	**2c**	**2t**	**2c**	**2t**
3c	75	40	82	39	84	69	98	16
3t	25	60	18	61	16	31	2	84

For intermediates **4c**, **4t**, **5c**, and **5t**, the sums of NBO charges of the dipole and dipolarophile parts were calculated. The sums of atom charges of dipole parts of **4c**, **4t**, **5c**, and **5t** are 0.73, 0.76, 0.72, and 0.78, and those of the dipolarophile parts of **4c**, **4t**, **5c**, and **5t** are −0.73, −0.76, −0.72, and −0.78, respectively.

Each of these intermediates is slightly more stable when computed with unrestricted density functional theory, which allows separate Kohn−Sham orbitals for α and β electrons. The spin density of the open-shell singlet wave function shows that the largest value of spin density resides on the C1 and C4. The spin densities of C1 in intermediates **4c**, **4t**, **5c**, and **5t** are 0.27, 0.21, 0.25, and 0.19, respectively. The spin densities of C1 in intermediates **4c**, **4t**, **5c**, and **5t** are −0.19, −0.17, −0.25, and −0.19, respectively. The calculated values of S^2 for intermediates **4c**, **4t**, **5c**, and **5t** are 0.18, 0.14, 0.21, and 0.13, respectively, indicative of some spin contamination by a higher-lying triplet diradical state. Therefore, the intermediates **4c**, **4t**, **5c**, and **5t** are both highly polarized zwitterions but are biradicals. The comparison of the RB3LYP single-point energies and the UB3LYP spin contamination energies also supports this conclusion. For intermediates **4c**, **4t**, **5c**, and **5t**, the RB3LYP single-point energies are only 0.3, 0.2, 0.4, and 0.2 kcal/mol, respectively, higher than the UB3LYP spin-contaminated single-point energies. The vertical singlet−triplet gaps of **4c**, **4t**, **5c**, and **5t** are 17.9, 19.5, 15.3, and 31.0 kcal/mol, respectively, larger than for hydrocarbon diradicals, which generally have nearly degenerate singlet and triplet states.[28]

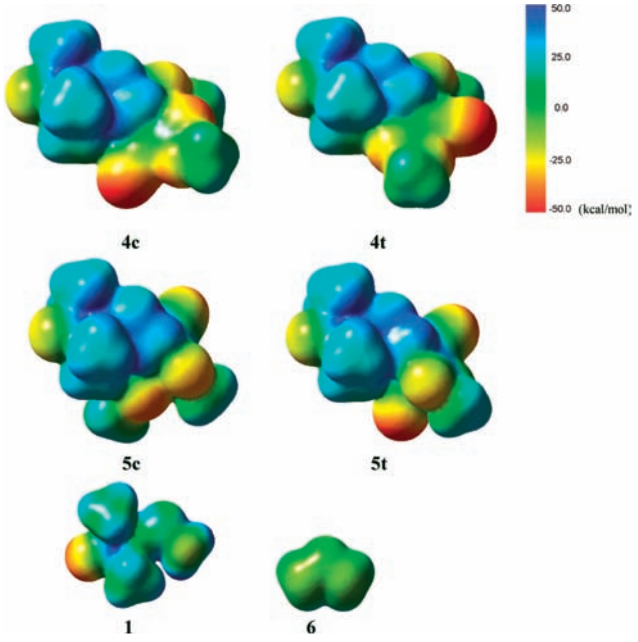

Figure 6. Electrostatic potential of **4c**, **4t**, **5c**, **5t**, **1**, and **6**.

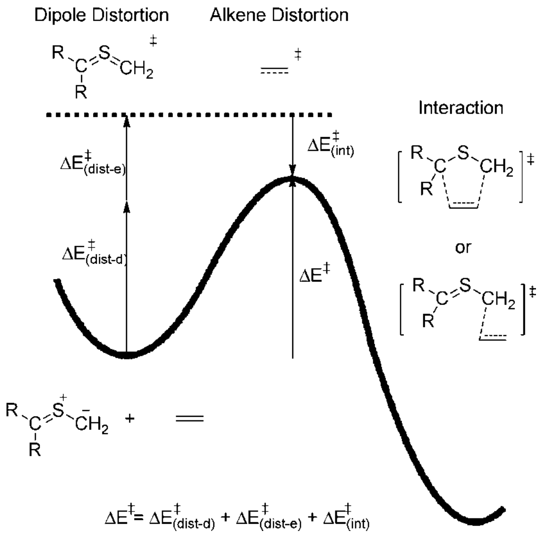

Figure 7. Relationship between activation, distortion, and interaction energies.

The electrostatic potentials of the dipoles **1** and **6** are also shown in Figure 6. The charge separation in dipoles **1** and **6** is small. The calculated values of S^2 for dipoles **1** and **6** are zero with UB3LYP. When dipole **1** reacts with a dipolarophile, the diradical character is increased. A single-point calculation of the dipolar part from intermediate **4c** leads to the calculated value of S^2 for the dipolar part in intermediate **4c** of 0.28. The spin densities of C1, S, and C2 for the dipolar moiety in **4c** are −0.43, 0.02, and 0.46.

6. Distortion and Interaction Energies for Concerted and Stepwise Mechanisms. The distortion−interaction energy model is a powerful tool to explain reactivity in bimolecular reactions (Figure 7).[12a,b,29] The activation energy ($\Delta E^\ddagger$) can be separated into the distortion energy of dipole ($\Delta E_{\text{dist-d}}$), the distortion energy of dipolarophile ($\Delta E_{\text{dist-e}}$), and the interaction energy between these distorted reactants (ΔE_{int}).

As shown in Scheme 5, both the stepwise (**23-ts**) and concerted (**24-ts**) transition structures can be located for the dipolar cycloaddition of Huisgen's thiocarbonyl methylide **1** to ethylene. Here the concerted transition structure, **24-ts**, is slightly lower in energy than the stepwise transition structure, **23-ts**.

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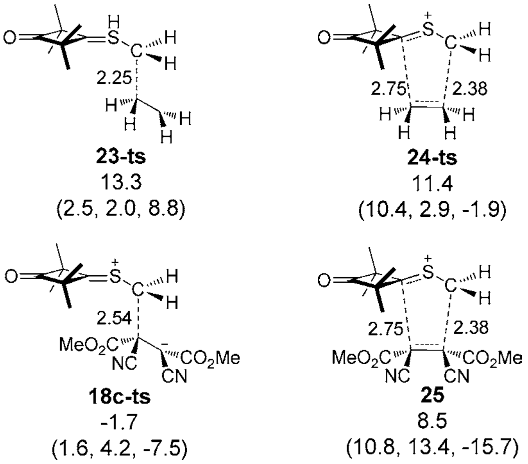
Scheme 5. Stepwise and Concerted Transition Structures for Reactions with Ethylene and with Dicyanomaleate[a]



[a] The values below the labels are the relative energies in the gas phase ($\Delta E^{\ddagger}$), and the values in parentheses are the distortion energy of dipole ($\Delta E_{\text{dist-d}}$), the distortion energy of dipolarophile ($\Delta E_{\text{dist-e}}$), and the interaction energy (ΔE_{int}).

The distortion and interaction energies were also calculated. Comparing the stepwise (**23-ts**) and concerted (**24-ts**) transition structures of the ethylene model, the distortion energy of the dipole part in the concerted transition structure **24-ts** is 7.9 kcal/mol higher than for the stepwise transition structure **23-ts**, indicative of the greater bending and pyramidalization of the dipole required to achieve the five-membered cyclic transition state. The interaction energy of the stepwise transition structure **23-ts** is 8.8 kcal/mol repulsive, while the concerted reaction has a small stabilizing interaction energy. The concerted transition structure **24-ts** is overall 2 kcal/mol more stable than the stepwise transition structure **23-ts**, due primarily to the large interaction energy.

The concerted transition structure of the dipolar cycloaddition of **1** with **2c** could not be located. To estimate the energy of this concerted transition structure, the constrained structure **25** was optimized. The two forming C−C bond lengths were set to the same lengths as in the concerted transition structure **24-ts**. The distortion energies of the dipole and dipolarophile in **25** are 9.2 kcal/mol better than in **18c-ts**. Although the interaction energy of **25** is 8.5 kcal/mol higher than for **18c-ts**, the calculated relative energy of **25** is 10.2 kcal/mol higher than for the stepwise transition state **18c-ts**, due to the large distortion energies in the former; this is mainly due to steric effects in the concerted transition structure.

The relative activation energy of **18c-ts** is 15.0 kcal/mol lower than that of **23-ts** due to the very low-lying LUMO energy of the dienophile. Comparing the distortion and interaction energies of **23-ts** and **18c-ts**, the distortion energies of **23-ts** and **18c-ts** are almost same, but the interaction energy of **18c-ts** is 16.3 kcal/mol higher than the interaction energy of **23-ts**.

Conclusion

The mechanisms for the 1,3-dipolar cycloaddition of a substituted thiocarbonyl ylide with highly electron-deficient dipolarophiles were analyzed with DFT computations. The computed mechanism is that deduced from experimental results by Huisgen et al.[4] The low stereoselectivity is due to the competition between ring closure and conformational processes of the intermediate. The intermediates are zwitterionic and open-shell species, previously referred to as polarized biradicals.[30]

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Supporting Information Available: Cartesian coordinates and energies of all reported structures, and complete ref 16. This material is available free of charge via the Internet at http://pubs.acs.org.

JA108432B

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